The above amendments to the specification and the claims do not add new matter to the application.

REMARKS

Claims 1-20 have been canceled and claims 21-36 have been added; as a result, claims 21-36 are pending. Support for new claim 21 may be found, for example, at claim 13. Support for new claims 22-26 may be found, for example, at claims 3-6. Support for new claim 27 may be found, for example, at claim 14. Support for new claim 28 may be found, for example, at claim 10. Support for new claim 29 may be found, for example, at page 5, paragraph 2. Support for new claims 30 and 31 may be found, for example, at claims 15-16. Support for new claims 32, 34, and 36 may be found, for example, at page 5, paragraph 2. Support for new claim 33 may be found, for example, at claim 17. Support for new claim 35 may be found, for example, at claim 18.

As a preliminary matter, the Examiner pointed out that an Information Disclosure Statement has not been filed. An Information Disclosure Statement, however, was filed by Applicant on April 9, 1998. A copy of the return postcard, date-stamped by the OIPE on April 13, 1998, is enclosed as evidence of receipt by the Patent Office. Also enclosed is a copy of the Information Disclosure Statement and 1449 Form. Applicant respectfully requests that the Examiner consider and make of record the cited references, and that a copy of the initialled 1449 Form be mailed to the undersigned attorney with the next official communication.

Claim 2 was rejected under 35 U.S.C. § 112, first paragraph, and the Examiner stated that the application does not provide enablement for compounds wherein the R^1 group is optionally interrupted by oxygen, nitrogen, sulfur, or phosphorous atoms. This rejection is respectfully traversed.

Although it is believed that claim 2 was fully enabled, the claims directed to compounds per say, including claim 2, have been canceled. However, the claim 2 definition for the compound of formula I has been amended and incorporated into claims 21, 28, 33, and 35. The amended definition does not recite that alkyl may be interrupted by nitrogen, sulfur or phosphorous. However, an R^1 alkyl may still be interrupted by oxygen. The pending claims are believed to be in compliance with 35 U.S.C. §112.

The mere possibility that a claim embraces inoperable embodiments does not render it unduly broad. In addition, it is not a function of the claims to specifically exclude all possible inoperative substances. As discussed by the Examiner at page 4 of the Office Action, the stability of peroxides and compounds comprising three contiguous oxygen is known in the art. Compliance with 35 U.S.C. §112 must be adjudged from the perspective that claims are addressed to a person of average skill in the particular art, who would not choose a combination that would render a claimed composition or method inoperative. Ex Parte Cole 223 USPQ 94 at 95-96 (copy enclosed). One skilled in the art would know, or could redially acertain, whether one of the recited oxygen interrupted alkyl groups would be stable. Accordingly, the Examiner is respectfully requested to find the pending claims to be in compliance with 35 U.S.C. §112, first paragraph.

Additionally, at page 4 of the Office Action, the Examiner states that dialkyl ethers are generally unreactive and unstable. This statement is unsupported by any evidence of record, and is believed to be inaccurate to the extent that it implys that dialkyl ethers are generally not suitable for use as pharmaceuticals.

Claim 2 was rejected under 35 U.S.C. § 112, second paragraph, due to the use of the word "may." This word has been deleted from the definition of R^1 in claims 21-33. The Examiner is respectfully requested to withdraw the rejection under 35 U.S.C.§ 112, second paragraph.

Claims 1-8 and 19-20 were rejected under 35 U.S.C. § 102(b) as being anticipated by Salerni et al., J. Chem. Soc., 1968, 12, 1399-1401. Claims 1-8 and 19-20 have been canceled.

Claims 10-15 and 17-18 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,079,262 (Kennedy) in view of Ariens. This rejection is respectfully traversed.

The Examiner has not established a *prima facie* case of obviousness.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the

references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. M.P.E.P. §2142.

The Examiner has not identified anything that would motivate one skilled in the art to combine the disclosures of Kennedy and Ariens. Additionally, even if Ariens discloses what the Examiner suggests (please see the next two paragraphs), the combination of references would not provide one skilled in the art a reasonable expectation that esters of ALA would have the same activity as ALA itself.

Finally, at page 6 of the Office Action, the Examiner asserts that Ariens "broadly" teaches how to modify part of a pharmaceutically active molecule that hinders tissue absorption by masking the offending functional group. In addition, the Examiner asserts that Ariens discusses 1) changing COOH groups to esters, 2) drug transport of an inactive "transport form" of a drug into an intercellular compartment, and 3) bioactivation of the drug by cleaving the masking moiety. The Examiner cited and provided pages 8 to 11 and 70 to 71 of Ariens to support this position.

Ariens (at pages 8 to 11 and 70 to 71) does not disclose the possibility of modifying a pharmaceutically active molecule that hinders tissue absorption by any means, and mentions nothing about masking an "offending" functional group. In addition, Ariens does not disclose changing COOH groups into esters; nor is there a disclosure of drug transport of an inactive form of a drug followed by activation by cleaving a masking moiety. Thus, the cited portions of Ariens do not contain any of the material suggested by the Examiner and do not support the rejection of the instant claims.

Thus, because there is no motivation to combine the cited references, because the cited references would not provide one skilled in the art with a reasonable expectation that ALA esters would have similar properties to ALA, and because the cited portion of Ariens does not disclose what the Examiner suggests it discloses, the Examiner has not established a *prima facie* case of obviousness.

The instant claims are not obvious over the cited references.

At pages 6 and 7, the Examiner asserts that it would have been obvious that ALA esters would penetrate the skin more easily than free ALA, since the formation of an ALA ester reduces the polar nature of ALA and allows better penetration of cell membranes. The Examiner goes on to state that once inside the cell, the alkyl groups are cleaved at physiological pHs to form the pharmaceutically active 5-ALA, i.e., the Examiner suggests the ALA esters are acting as pro-drugs for ALA. Applicant respectfully disagrees with the Examiner for the reasons discussed below and in the accompanying Declaration.

First, one skilled in the art would not assume that esterification of 5-ALA would provide a compound that would penetrate cell membranes more redially than free 5-ALA. The Examiner's suggestion assumes that ALA and ALA esters penetrate cell membranes by passive diffusion. This assumption is not valid in view of what is known about the transport of ALA through cell membranes. Details of this are set out in points 8 to 10 of the enclosed Declaration. It is known that 5-ALA (an endogenous amino acid) is transported by active amino acid transport systems, not by passive diffusion. Therefore, it would not be expected that a non-endogenous derivative, such as a 5-ALA ester, would be transported by the natural transfer systems. Thus, it would have been counter-intuitive to make esters of 5-ALA.

In addition, even if 5-ALA ester did penetrate the cell membrane by passive diffusion, it would be expected that such passive diffusion would be less efficient than a natural endogenous active transport mechanism and would not provide sufficient quantities of a photochemotherapeutic agent within a cell. Thus, the fact that the uptake of the ALA esters into cells was found to be better than the uptake of 5-ALA is unexpected.

In further support of the the patentability of the instant claims, the following unexpected properties of ALA esters are discussed in the enclosed Declaration or in the Specification.

1. ALA esters, in contrast to free ALA, are not transported by the blood to other tissues. Such properties of the ALA esters are advantageous for PDT, and would not be predicted if ALA esters act as pro-drugs for ALA.

2. ALA esters display a significantly increased selectivity for tumor tissues versus surrounding non-tumor tissue, compared with free ALA. Again, such increased selectivity would not be predicted if ALA esters act as pro-drugs for ALA.
3. In clinical trials, much less severe pain is felt by patients treated with ALA esters than by those treated with ALA alone. The reason for this significant and unexpected phenomenon has not been ascertained, but may be explained by the different transport mechanisms of ALA and ALA esters.
4. ALA esters are better able to penetrate skin and other tissues than ALA and the penetration is deeper and faster.
5. ALA esters are better enhancers of PpIX production than ALA.

The results demonstrating the latter two advantages are disclosed in the specification as filed.

The above points demonstrate that ALA esters possess advantageous and unexpected properties compared to ALA. Thus, the claimed invention is not obvious over the disclosures of Kennedy and Ariens. In light of the above remarks and the enclosed Declaration, the Examiner is requested to reconsider and withdraw the rejection over Kennedy and Ariens.

Claim 9 was rejected under 35 U.S.C. § 103(a) as unpatentable over Morrison et al., Organic Chemistry, 3rd Edition, Allyn and Bacon, Boston, 1973. Claim 9 has been canceled.

Claim 16 was rejected under 35 U.S.C. § 103(a) as unpatentable over Kennedy and Ariens in view of U.S. Patent No. 4.,575,515 (Sandborn). This rejection is respectfully traversed.

As discussed above, the ALA esters recited by the instant claims possess unexpected and advantageous properties over ALA. Thus, the instant claims are patentable over the cited references. Thus, the Examiner is respectfully requested to reconsider and withdraw this rejection.

Conclusion

In view of the above amendments and remarks, reconsideration and withdrawal of the rejections of the claims of the above-identified application is respectfully requested.

Applicant submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612)-359-3265 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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By their Representatives,

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Date 30 June 1999 By _____

Robert J. Harris, Ph.D.
Reg. No. 37,346

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Assistant Commissioner of Patents, Washington, D.C. 20231 on **June 30, 1999**.

Robert J. Harris _____
Name Signature